c) comparing the level of MLK activity in the presence of the compound with the level of MLK activity in the absence of the compound, wherein a decrease in MLK activity in the presence of the compound is indicative that the compound has an ability to inhibit MLK activity;

d) contacting the compound having an ability to inhibit MLK activity with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is kinase activity; and

e) comparing the occurrence of apoptosis in the cultured neuronal cells in the presence of the compound with the occurrence of apoptosis in the cultured neuronal cells in the absence of the compound;

wherein the compound having an ability to inhibit MLK activity has the ability to prevent neuronal cell death when the occurrence of apoptosis in the cultured neuronal cells in the presence of the compound is less than the occurrence of apoptosis in the cultured neuronal cells in the absence of the compound.

REMARKS

In response to the Official Action of October 1, 2001, made final, applicant has submitted an Amendment after Final Rejection in this application. In the Amendment, certain claims were cancelled, and other claims were amended, in an effort to place this application in condition for allowance.

In response to the prior Amendment, an Advisory Action dated March 21, 2002, was mailed by the Examiner. In the Advisory Action, the Examiner maintained the rejection of the claims on the basis that the proposed claim amendments could not be entered. In particular, the Examiner states that, as amended, claims 7 and 8 are directed to *in vivo* conditions, while claim 1, on which claims 7 and 8 depend, is directed to *in vitro* conditions. Further, the Examiner has pointed to certain errors in the claims as a result of the proposed amendments.

Applicant has now cancelled claims 7 and 8. Cancellation of these claims is for the purpose of advancing the prosecution of this application by delineating allowable subject matter, and should not be construed as a relinquishment of the subject matter covered by these claims. In addition, the inconsistency noted with respect to claim 14 has now been corrected. Accordingly,

applicant respectfully submits that the present amendment resolves all of the outstanding issues raised by the Examiner in the Advisory Action, and serves to place this application in condition for allowance.

In the Official Action of October 1, 2001, the Examiner has restated her position that the present application is not entitled to the benefit of the filing date of the provisional application. Applicant has again reviewed the text of the provisional application, and for the reasons discussed in more detail below, believes that it is fully entitled to the benefit of the provisional application priority date with respect to all claims now presented in this application. Accordingly, the Examiner is respectfully urged to reconsider and reverse the denial of the benefit of the priority date.

The claims of this invention are directed to methods for assessing the ability of a compound to preventing neuronal cell death, and/or for inhibiting MLK activity. For purposes of comparing the provisional and regular applications, the methods of this invention involve the steps of (1) contacting the compound with cultured neuronal cells, or an MLK protein and a substrate for the protein, (2) measuring the response of the cells or protein substrate to the compound, and (3) comparing these results to a control. The issue regarding benefit is whether these methods are disclosed in sufficient detail in the provisional application in order to place one skilled in the art in possession of the claimed invention in compliance with the requirements of the first paragraph of 35 U.S.C. §112. Applicant submits that this is the appropriate standard for benefit purposes, and that applicant has fully complied with this standard.

The provisional application states that polyglutamine-expanded huntingtin causes neuronal toxicity in, for instance, cultured HN33 neuronal cells. As a comparison, 293 cells were also evaluated. See pages 7 and 8 of the provisional application, and note than there is no limitation in the independent claims as to the type of compound that can cause such toxicity. Thus, the term "compound", as used in the invention, includes both normal huntingtin and mutated huntingtin within its scope. Moreover, the cells of the invention have activated MLK2 activity as required by the claims. Applicant submits that one skilled in the art, upon reading the provisional specification, would understand that normal huntingtin has the ability to inhibit neuronal cells death in cells with activated MLK 2 activity which are contacted with normal huntingtin, since such cells survive. This satisfies the limitations of the independent claims of the present invention. See the relevant disclosure in the provisional application at pages 6-7, and

compare Figures 4B and 4C. The provisional application discloses the use of normal huntingtin as only one example of a suitable compound, as one skilled in the art would readily appreciate.

In addition to cell based methods, the provisional application also discloses the use of cell free methods for assessing the relationship of a particular compound to neural toxicity. On page 5, the provisional application states that MLK is a protein kinase that directly binds to and activates SEK1. The expression of mutant huntingtin in MLK-expressing neuronal cells induces cell death. However, when a dominant negative form of SEK1 is co-expressed with mutated huntingtin in MLK-expressing neuronal cells, the death of the cells is blocked. Accordingly, one of ordinary skill in the art would understand that active MLK kinase activity, in binding to and activating SEK1, results in neuronal cell death, and that a compound, such as normal huntingtin, that inhibits MLK2 kinase activity, and the activation of the MLK substrate SEK1, also inhibits neuronal cell death.

Although the present claims may not be supported in *ipsis verbis* by the disclosure in the provisional application, an exact written description not a necessary precondition for benefit under 35 U.S.C. 112, first paragraph. All that is required is that one skilled in the art be placed in possession of the invention, and applicant has done so here.

For all of these reasons, applicant believes that the provisional application fully supports the full scope and range of the present claims, including both cell based and cell free methods, and that the instant application is therefore fully entitled to the benefit of the May 14, 1998 priority date.

In the Official Action of October 1, 2001, claims 1-3, 5-8, 9-10, 12-19 and 45 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement in the specification. In particular, the Examiner states that the specification does not disclose DLK and LZK activity, and does not provide enablement for the treatment of a mammal susceptible to or having a neurological condition. The Examiner also states that the claims are directed to activities which are unsupported by the specification. This ground of rejection is traversed.

In order to expedite the prosecution of this application, the claims have now been amended to exclude DLK and LZK activity, and to delete the remaining language which has been objected to. Accordingly, the amended claims are now believed to be in full compliance with all of the requirements of 35 U.S.C. 112, first paragraph.

Claims 2, 7-9 and 12-13 have also been objected to under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. This ground of rejection is traversed.

The claims have been amended to correct the Markush language, and to delete identical claims. In addition, the claims are now believed to overcome the objection concerning the further limitation of the claimed method.

Claims 1, 6, 14, 19 and 45 have been rejected under 35 U.S.C. 102(e) as being anticipated by Miller et al. This ground of rejection is traversed.

The Examiner states that this rejection is proper since MEKK1 phosphorylates SEK1, and that this property meets the limitation of the claims concerning an activity having the ability to bind a SEK1 protein.

Applicant notes that this limitation has now been removed from the claims. Accordingly, this rejection has been obviated.

Claim 19 also stands rejected under 35 U.S.C. 103(a) as obvious over Tibbles et al., Rana et al. and Hirai et al., each in view of Au-Young et al. This ground of rejection is also traversed.

This rejection also appears to be based on the claim limitation concerning the ability to bind a SEK1 protein. Since this limitation has been removed from the claims, this rejection has also been obviated.

In view of the foregoing facts and reasons, this application is now believed to overcome the remaining rejections, and to otherwise be in proper condition for allowance. Accordingly, withdrawal of the rejections, and favorable action on this application is solicited. Entry of this Amendment is deemed appropriate at this time since the amendments are responsive to the rejection and advisory action, are a genuine attempt to advance the prosecution of the application, and do not require any further search or consideration on the part of the Examiner.

The Examiner is invited to contact the undersigned at the telephone number listed below if this is believed to facilitate allowance of this application.

Respectfully submitted,

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MARKED-UP CLAIMS

1. (Five Times Amended) A method for assessing a compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a compound with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is selected from the group consisting of MLK1 activity, MLK2 activity, and MLK3 activity, and wherein the activity is a kinase activity [DLK activity, LZK activity, and an ability to bind a SEK1 protein]; and

(b) determining the number of cultured neuronal cells that die;

wherein a decreased number of dead cultured cells in the presence of the compound compared to the number of dead cultured neuronal cells in the absence of the compound is indicative of the compound's ability to prevent neuronal cell death.

2. (Three Times Amended) The method of claim 1, wherein the neuronal cells [are expressing] express a mutated protein selected from the group consisting of polyglutamine stretch-expanded huntingtin [or] and C-terminal 100 amino acids of amyloid precursor protein, or the neuronal cells are treated with a neurotoxin to induce apoptosis.

9. (Four Times Amended) A method for assessing a compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a compound with cultured neuronal cells expressing a mutated protein selected from the group consisting of polyglutamine stretch-expanded huntingtin [or] and C-terminal 100 amino acids of amyloid precursor protein, or with neuronal cells treated with a neurotoxin to induce neuronal cell death; and

(b) determining the number of cultured neuronal cells that die;

wherein a decreased number of dead cultured neuronal cells in the presence of the compound compared to the number of dead cultured cells in the absence of the compound is indicative of the compound's ability to prevent neuronal cell death.

14. (Five Times Amended) A method for assessing the ability of a compound to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a compound with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is selected from the group consisting of MLK1 activity, MLK2 activity, and MLK3 activity, and wherein the activity is a kinase activity [DLK activity, LZK activity, and an ability to bind a SEK1 protein];

b) contacting, in the presence of the compound, surviving cells from step (a) with an agent that induces apoptosis; and

(c) comparing the level of apoptosis in the cells in the presence of the compound with the level of apoptosis in the cells in the absence of the compound;

wherein the compound is a potentially useful drug for treating mammals when the level of apoptosis in the cells in the presence of the compound is less than the level of apoptosis in the cells in the absence of the compound.

19. (Four Times Amended) A method for assessing a compound's ability to inhibit MLK activity, comprising:

a) contacting a compound with a MLK protein and a substrate therefore, wherein the MLK protein is selected from the group consisting of MLK1, MLK2, and MLK3, [DLK, LZK] and combinations thereof;

b) measuring the level of MLK activity, wherein the MLK activity is a [selected from the group consisting of] kinase activity [and an ability to bind a SEK1 protein]; and

c) comparing the level of MLK activity in the presence of the compound with the level of MLK activity in the absence of the compound, wherein a decrease in MLK activity in the presence of the compound is indicative that the compound has an ability to inhibit MLK activity.

45. (Amended) A method for assessing the ability of a compound to inhibit MLK activity and to prevent neuronal cell death, comprising the steps of:

a) contacting a compound with a MLK protein and a substrate therefore, wherein the MLK protein is selected from the group consisting of MLK1, MLK2, and MLK3, and combinations thereof;

b) measuring the level of MLK activity, wherein the MLK activity is a kinase activity [selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein];

c) comparing the level of MLK activity in the presence of the compound with the level of MLK activity in the absence of the compound, wherein a decrease in MLK activity in the presence of the compound is indicative that the compound has an ability to inhibit MLK activity;

d) contacting the compound having an ability to inhibit MLK activity with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is a kinase activity [selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein]; and

e) comparing the occurrence of apoptosis in the cultured neuronal cells in the presence of the compound with the occurrence of apoptosis in the cultured neuronal cells in the absence of the compound;

wherein the compound having an ability to inhibit MLK activity has the ability to prevent neuronal cell death when the occurrence of apoptosis in the cultured neuronal cells in the presence of the compound is less than the occurrence of apoptosis in the cultured neuronal cells in the absence of the compound.